REMARKS

STATUS OF THE CLAIMS

Claims 1-2, 9, 15-16, 31-33, 39, 43, 66, 69-70, 77, 97 and 107-117 are pending in the application. All other claims are cancelled.

The amendments to independent claims 1, 39 and 69 are provided to clarify the claims to more clearly reflect the Examiner's stated understanding of claim scope, as helpfully articulated in the Advisory Action.

New claims 107-115 are essentially similar to previous claims 98-106, except for adjustments to provide proper claim dependency, and except that the Markush groups have been limited to the elected restriction group.

New claims 116-117 find support, e.g., at paragraphs 28 (where the term sense nucleic acid is defined), paragraph 39 (where lycopene β-cyclase and lycopene ε-cyclase are identified as regulators of carotenoid expression), paragraph 71, where the relevance of these enzymes in the various carotenoid synthetic pathways is taught, and at paragraphs 131-143, where various RNAi and antisense procedures for modulating carotenoid levels, including for the accumulation of lycopene are taught (see, e.g., paragraph 139).

No new matter is introduced by the amendments or new claims.

RESTRICTION

The Examiner correctly indicates in the Advisory Action that Applicants restriction election was made with traverse. However, the Action also argues that reasons for traversal were not presented. Applicants note that highly detailed reasons for traversal of the various requirements in the subject case were made in their responses of October 3, 2007 and January 24, 2008. These detailed reasons were unaddressed in any subsequent requirement. The given reasons for traversal are equally applicable to the restriction of May 16, 2008. Specifically, as argued, the restriction groupings are not reflective of the actual claims, breaking the claims into various arbitrary groups based on limitations imposed by the Examiner, rather than present in the claims. The requirement should be phrased as an election of species, rather than as a restriction requirement. Finally, the

requirement ignores the possibility of combining different types of regulators to achieve an effect on carotenoid levels, a possibility covered by the claims, and simply not provided for in any restriction group. Applicants, accordingly, maintain their traversal of the current requirement for the reasons of record.

In addition to the reasons of record, the groupings fail on technical/logical grounds. For example, Group IV, the elected group, is "drawn to a method of *decreasing* carotenoid accumulation in a pineapple plant using sense, antisense or dsRNA..." Group I, in contrast is drawn to a method of "*increasing* carotenoid accumulation in a pineapple plant using sense, antisense or dsRNA..."

The technical problem with this grouping is that an antisense or dsRNA does not necessarily just "decrease" or just "increase" carotenoid accumulation. In fact, antisense or dsRNA constructs typically both increase *and* decrease carotenoid accumulation, at the same time. That is, blocking expression of one enzyme in a pathway required for production of a carotenoid reduces the accumulation of that carotenoid. However, blocking the enzyme also *increases* accumulation of carotenoids produced upstream of the enzyme. For example, lycopene β-cyclase converts lycopene (which is a carotenoid) to β-carotene (also a carotenoid). Inhibiting lycopene β-cyclase results in an *increase* in lycopene levels, as well as a *decrease* in the production of, e.g., β-carotene. This strategy is described, e.g., at paragraph 138-139 of the subject application.

Thus, at least groups I and IV should be combined. Applicants note that a single group must cover both increasing and decreasing carotenoid accumulation using sense or antisense gene suppression, because both typically occur as a result of expression of the *same* regulator. Similar logic applies to the recombination of groups II and V and groups III and VI.

ENABLEMENT REJECTION UNDER 35 USC 112

Claims 1-2, 9, 15-16, 31-33, 66, 69- 70, and 77 were rejected under 35 USC 112, paragraph 1 (enablement). To the extent that the rejections apply to the amended or new claims, Applicants respectfully traverse for the reasons of record and for the additional reasons noted below.

The Advisory Action argues that the specification examples with respect to both anti-sense and RNAi based suppression of carotenoid enzymes in pineapple are prophetic, and therefore not enabled or described.

As an initial matter, the use of prophetic examples is permissible, and can be used to teach one of skill how to practice an invention. See, e.g., Atlas Powder Co. v. E.I. du Pont De Nemours and Company 224 USPQ 409 (Fed. Cir. 1984); Ariad Pharmaceuticals, Inc., Massachusetts Institute of Technology, the Whitehead Institute for Biomedical Research, and the President and Fellows of Harvard College v. Eli Lilly and Company (Fed. Cir. 2009), Slip opinion at page 7.

Moreover, Applicants also provide herewith a declaration of Dr. Ebrahim Firoozabady, unequivocally demonstrating the production of extra golden, pink, and pink/extra golden pineapple fruits, using the methods set forth in the subject application.

This declaration includes a demonstration that three different types of carotenoid biosynthetic modulators that fall within the scope of the claims all provide altered carotenoid levels in pineapple. These include:

(1) plants that express a heterologous phytoene synthetase gene from tangerine, producing more β-carotene than corresponding commercial pineapple cultivars (giving the pineapple fruits a deep golden color);

(2) plants that express an suppressive RNAi against endogenous pineapple beta lycopene synthase, accumulating excess lycopene (giving the fruits a reddish pink color), and suppressing production of downstream carotenoids such as β-carotene;

(3) plants that express a heterologous phytoene synthetase gene from tangerine and that also express a suppressive RNAi against endogenous beta lycopene synthase, resulting in fruits that are reddish pink and golden in color.

Applicants note that the declaration includes high photo-quality color reproductions. If the Examiner has trouble accessing the original documents, please contact the undersigned to arrange for direct transmission of the reproductions, or electronic files thereof, to the Examiner.

Applicants note that one of skill would merely have had to follow the directions in the Application to achieve the claimed invention. The invention is,

therefore, clearly enabled. Indeed, taking each of the "Wands" factors into account plainly shows this, as discussed in more detail below.

The Claims are Enabled Under the Standard Articulated by Wands—Undue Experimentation is Not Required

The Action alleges that the invention fails to meet the enablement standard articulated by In Re Wands 8USPQ2nd 1400 (Fed Cir 1988). As identified by the Examiner, the Wands case sets forth a classic multi-part analysis to be used for determining whether undue experimentation is required in practicing a claimed invention. In understanding how each of the features of this analysis should be applied to the present case, it is instructive to examine the facts and holdings of Wands, to understand how the facts of the present case can be compared to the Wands case and how these facts fit into the framework of the Wands analysis. As will be shown in detail below, it is plain that the present invention more than meets the requirements to provide enablement as articulated by Wands.

The claim at issue in Wands was an immunoassay method claim with two steps: first, a test sample containing a hepatitis B-surface antigen was contacted with an antibody, and second, the resulting substance was detected (using the antibody). The antibody was specified as having a binding constant of 10^9 /M. No structural recitation of the genus of antibodies that could be used in the test was provided, nor, indeed, was *any* structural recitation of even a single specific antibody provided in the application. The Patent Office argued that the production of high affinity antibodies was unpredictable, and, therefore, that undue experimentation would have been required to practice the invention. The Court disagreed and struck down the PTO's rejection, setting forth a framework for the analysis to be followed by the Office in the future when assessing whether undue experimentation is required in the practice of the invention.

Wands Factor 1—The Quantity of Experimentation is reasonable and is no more than was the case in Wands

The first factor identified by the Court was "the quantity of experimentation necessary" to practice the claimed invention. In its analysis, the Court first noted that the experimental process for making antibodies that bound the relevant antigen were set forth in the application. In essence, this process included an elaborate hybridoma fusion screening and manipulation procedure, followed by a binding screen to

identify "high binders" followed by another screening procedure to identify what type of antibody had been generated (IgM being the desirable antibody type in Wands). The PTO argued that less than 3% of hybridomas that were created produced antibodies, and of these, only 20% produced IgM antibodies. The first four hybridoma fusion experiments performed by the Wands inventors were failures, with the next 6 being successful. The Court held that this was not evidence of unpredictability, particularly given that the technique at issue was in general use for antibody production. Wands at 1406.

In the present case, the type of "experimentation" at issue is also set forth in the Application and is entirely routine. As taught in the application, one of skill transforms pineapple with a putative carotenoid expression regulator, grows the pineapple plant, and then screens the pineapple fruit via simple visual inspection to identify effects on carotenoid accumulation. Entire crop fields of transformants can easily be screened by this straightforward method. As in Wands, the type of experimentation is precisely what one of skill in the relevant field expects to do, i.e., screening transformants for specific and easily detectable changes in phenotype. This is what a plant molecular biologist/ crop breeder does for a living—there is nothing remotely unreasonable about expecting one of skill to screen for a simple visually inspected crop trait.

Wands Factor 2: The Direction or Guidance Provided is Extensive

The second factor identified by Wands was the amount of direction or guidance presented. The Wands court indicated that the Wands specification provided considerable guidance. In the present case, Applicants have identified the relevant carotenoid enzyme targets, and have identified several detailed strategies for modulating enzyme expression. These targets function as taught in the application, as further shown by Dr. Firoozabady's declaration. Given the high level of skill in the art (discussed below) the instructions in the application for practicing the invention are plainly sufficient.

Wands Factor 3: Working Examples

The third factor identified by Wands is a restatement of part of the second factor, i.e., the presence or absence of working examples. Applicants provided a detailed

past-tense working example of the production of a pineapple transformed with a carotenoid modulator (the tangerine psy gene), falling within the scope of the claims at issue. Furthermore, Applicants provided a detailed description of how to produce other modulator-transformed pineapple, including the use of sense and anti-sense constructs against carotenoid enzyme targets. Applicants have proven that these descriptions are accurate, i.e., that targeting carotenoid synthetic genes results in changes in carotenoid accumulation (*see*, accompanying declaration of Dr. Firoozabady). In particular, inhibiting expression of lycopene β-cyclase was identified in the application as a particularly desirable target to increase lycopene accumulation (see, e.g., paragraph 139). This strategy was shown to be effective to increase lycopene accumulation, producing unique and commercially valuable reddish colored pineapple fruit.

Wands Factor 4: The Nature of the Invention

The fourth factor identified by the Wands court is the "nature of the invention." Wands indicates that, "the nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners in this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." Wands at 1406. The Office alleged that the success rate of such screening for antibodies was just 2.8%, which the Court largely disagreed with, but also indicated that even such a low success rate would not lead to a conclusion of undue experimentation. Wands Fn 29.

The nature of genetically modified plant technology is to introduce a gene of interest into a plant and to screen progeny for a phenotype of interest. So far, carotenoid levels have been modulated in a wide variety of ways, to achieve different types of carotenoid accumulation. The "success" rate is, so far, higher than in Wands. Furthermore, the type of screening that is necessary to practice the invention is precisely what is expected in the field.

Wands Factor 5: The State of the Prior Art

The fifth factor identified by the Wands court is the state of the prior art. Wands indicated that the state of the prior art was advanced, with "all of the methods required to practice the invention being known." This is true for the present case as well. While Applicants do teach new methods of pineapple transformation (e.g., direct

organogenesis), the actual steps of these methods are straightforward plant transformation and culture techniques.

Wands Factor 6: The relative Skill of Practitioners in the Field

The sixth factor identified by Wands is the relative skill of practitioners in the field. The level of skill of practitioners in the field was considered "high" for the Wands decision. Obviously, it is much higher now than it was in 1988. The information that biotechnology practitioners are presumed to be aware of has had over 20 years to develop, and the pace of development during that period has been staggering. A typical researcher can, for example, transform and screen large numbers of transformants by techniques that were entirely unavailable 20 years ago. If the level of skill in the art was "high" at the time of Wands then it is now positively stratospheric. In any case, a competent plant molecular biologist, given Applicants' disclosure can certainly perform each and every step required to practice the claimed methods.

Wands Factor 7: The Predictability or Unpredictability of the Art

The seventh factor identified by Wands is the unpredictability of the art. In Wands, the Patent Office had argued that the "low" observed 2.8% rate of success in screening for antibodies in the case was evidence of unpredictability. However, the Court took a different view, noting that in several of the cases in which an entire overall antibody production screen was performed, at least one antibody was produced.

In the present case, the Examiner's central argument is that Applicants did not present past-tense working examples for certain types of modulators (e.g., RNAi) falling within the scope of the claims (though other types of modulators are presented as past-tense working examples). Applicants have now provided declaration evidence that unequivocally proves that the strategies for producing these modulators, as taught in the specification, do work. In practice, the invention has proven to be predictable, with a wide variety of modulators displaying the ability to modulate carotenoid accumulation.

The Breadth of the Claims is commensurate with Applicant's Teachings

The eighth factor identified by Wands was the breadth of the claims. In Wands, the claims essentially covered the entire universe of possible antibodies, including any isotype, that specifically bound Hepatitis B surface Antigen. The Office

argued that this claim was unduly broad because only a few examples (three or four, depending on how one interprets the case), out of 143 hybridomas that were disclosed, were shown to fall within the scope of the claim. That is, the Office (and Judge Newman's dissent) argued that because there were only four working examples (out of 143 hybridomas produced), the scope of the claimed invention had not been enabled. The (controlling) majority for the case dismissed this out of hand, noting that the fact that additional hybridomas had not been screened was hardly equivalent to a showing that the hybridomas did *not* meet the limitations of the claims. Wands at 1406. Thus, the court held that a claim covering the entire universe of potential antibodies that bound the given antigen was not unduly broad because it *had* been shown that antibodies meeting the limitations of the claims clearly could be produced by the relevant antibody screening methods (there were working examples provided). Thus, the teachings were commensurate with the scope being claimed.

This also has a precise logical correlate to the present case—while Applicants claims are broad, it has been unquestionably proven that many different carotenoid modulators work in the methods of the application. These include the introduction of heterologous carotenoid synthetic genes, RNAi knock down of endogenous carotenoid synthesis genes, and combinatorial constructs that include both heterologous and RNAi knockdown constructs.

Conclusions regarding Enablement

The analysis of the Wands factors, taking the true nature of the analysis as applied to the classic Wands case and Applicant's claims clearly shows that Applicants have taught one of skill how to make and use the invention. Indeed, in every relevant analysis, the present case more than meets the standard articulated by the Court. This rejection must be withdrawn.

WRITTEN DESCRIPTION REJECTION UNDER 35 USC 112

Claims 1-2, 15, 16, 31-33, 39, 43, 66, 69, 70, 77 and 97-106 were rejected for alleged lack of written description.

The crux of the Examiner's argument is that Applicants allegedly did not provide all possible *structures* of RNAi and antisense constructs that are active in pineapple to block the expression of carotenoid synthetic enzymes (thereby modulating

carotenoid levels). Applicants respectfully submit that this entire line of analysis is based on a flawed understanding of the law, and is also based on a flawed understanding of the *claimed* invention.

First, the law is quite express that examples of particular structures are *not* required to support adequacy of written description. Falko-Gunter Falkner v. Inglis 79 USPQ2d 1001, 1007-1009 (Fed Cir. 2006), Cert. denied 549 U.S. 1180, 127 (Supreme Court, 2007):

> (1) Examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met ... even when actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure...

Moreover, Applicants are not claiming *particular* RNAi or antisense *constructs*. Instead, they are claiming *methods* of controlling carotenoid accumulation. These methods can use any of a wide variety of carotenoid genes, antisense, RNAi, or other constructs, as detailed in the application. The Application provides detailed information regarding a variety of carotenoid synthetic genes, as well as a clear identification of which genes are particularly good targets for either over expression or suppression via RNAi or antisense. Indeed, many known genes that can be adapted to the methods of the invention are described, e.g., between paragraphs 79 and 90. Detailed strategies for making RNAi and antisense constructs (among others) are described at paragraphs 131-143. This is sufficient to demonstrate possession of the *claimed* invention. The rejection should be withdrawn.

TERMINAL DISCLAIMER AND DOUBLE PATENTING

Applicants note that a terminal disclaimer will be filed, overcoming the obviousness-type double patenting rejection with respect to USSN 10/536,885, once the claims are otherwise in condition for allowance, assuming a disclaimer is appropriate at that time. Please contact the undersigned to arrange for expedited submission of a terminal disclaimer.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, **a telephone interview with the Examiner is hereby requested.** Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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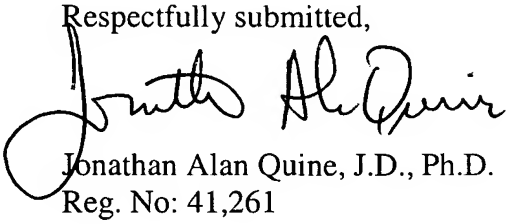
Respectfully submitted,



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Attachments:

1) A transmittal sheet;
2) A Fee Transmittal Sheet;
3) A Petition for Extension of Time for 2 Months;
4) Request For Continued Examination;
5) Appendix A: Figure of transformed pineapple (in color);
6) Appendix B: Declaration of Dr. Ebrahim Firoozabady; and
7) A receipt indication postcard.